Quarterly Progress Report

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Neural Prosthetic Control

NINDS CONTRACT

Department of Neuroscience and Brain Science Program

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Contents

This Quarterly Report is organized into five sections. First there is a summary of the overall objectives of the contract. In the subsequent three sections we describe the goals and activities of the three main components of the project: Array development, development of decoding algorithms, and development of interfaces. Each section has, at its end, a description of the progress made during the current quarter on that phase of the project. Lastly, we describe project goals for the upcoming quarter.

1. Introduction

A number of neurological disorders, such as spinal cord injury, MD and ALS result in the inability to make voluntary movements. A major reason for paralysis in these disorders is a disconnection of the signal from a normal brain from the spinal cord or muscles. Devices that can detect and decode motor commands have the potential to restore voluntary actions in these individuals. The purpose of this project is to demonstrate the ability to use neural signals to control real world devices in monkeys; such devices can ultimately serve as prosthetic aids for paralyzed individuals.

Control signals for prosthetic devices can be derived from a number of sources, including the eyes, muscles, and EEG. These signals are, however, rather limited in the number of dimensions they can control. Going beyond a one dimensional control signal is difficult and often interferes with natural behavior. For example, two dimensional EEG control requires full attention to control without distraction (such as gaze shifts). By contrast, populations of neurons appear to contain rich signals, potentially able to control multiple dimensions independently. However, chronic recording of multiple neurons in primates has been technically challenging, the ability to decode neural activity into meaningful control signals is poorly understood and the ability to control devices using such signals is not developed.

The overall goal of this work is to develop a means to bring a robotic arm under near real time neural control using a multineuron signal derived from a recording device that is chronically implanted in a macaque monkey motor cortex. This project has three specific objectives. The **first objective** is to develop and test technologically advanced neural recording devices in a non-human primate model. This work examines the stability, efficiency and biocompatibility of electrode arrays and the suitability of the primary motor cortex as a sight to obtain neural recordings. Once recorded, neural activity must be decoded into meaningful control signals. The optimal methods for such decoding are not obvious. A **second objective** of the project is to examine various decoding methods and evaluate their ability to be useful control signals. This requires mathematical tools and signal processing that reconstructs intended actions from abstract, neurally based motor commands generated in the cortex. This aspect of the project involves fundamental motor control questions, such as what coordinate system is used to encode voluntary actions. **A third objective** of this project is to show that such signals can be used to control devices such as a robotic arm or a computer interface. These devices serve as a proxy for the lost limb and can be used to recreate useful actions like those intended for the arm. Successful completion of these goals would suggest that this approach could be used to restore movement in paralyzed humans.

2. Summary of Achievements this quarter Significant progress was made in all three objectives during the past quarter. We implanted three additional arrays, further developed methods to enhance the speed of training monkeys for use in array testing, and perfused two monkeys for histological processing. Histological material from an additional monkey was examined. We continued development of neural decoding methods, including new probabilistic methods. We also continued work on the interface with the CRS robotic arm, which now can initiate movement from neural data in <200ms, but with some variability.

Real time control of a computer cursor by a monkey was achieved and we began testing methods for transient inactivation of the arm.

3.0 Array Development

The goal of the array development of this aspect of the project is to identify the optimal properties and implantation procedures for Bionic/Utah electrode arrays to ensure long term, reliable recordings in macaque monkey cortex. This requires monkey training in various behavioral tasks, implantation using various modifications in the surgical procedures and in the array assembly and recording to test the quality and stability of units.

3.1 Behavioral training In order to test for motor related neural activity, monkeys are first operantly conditioned to the various arm movement tasks using juice or water reward. Animals are motivated to perform these tasks by restricting access-time to fluids. During training and recording periods, monkeys are allowed as much fluid as they wish to obtain when they perform the training tasks. Fluids are also supplemented after training sessions and on weekends. as approved by the institutional animal care committee. Training tasks are also support the animals' psychological well-being because they provide an additional sources of challenge with positive reinforcement.

3.1.1 Radial direction task: Monkeys are first operantly conditioned (using juice or water reward) to perform an instructed-delay task consisting of visually-guided planar reaching movements from a central holding position to a radially located target (Figure 3). Animals move a two-joint manipulandum in the horizontal plane to direct a cursor from a central hold position to one of eight possible radially positioned targets (6 cm away from start position) viewed on a computer monitor. Hand position is recorded as the x and y location of the manipulandum using a digitizing tablet, with a sampling rate of 200 Hz. The tangential velocity and acceleration of the hand is computed by numerical differentiation using own custom software. A trial is composed of three epochs: a "hold" period during which time the monkey maintains the cursor at the hold position for 0.5 s, a random 1-1.5 s "instructed delay" period during which the target for the forthcoming action appeared but movement is withheld, and a "go" period initiated by target blinking (mean reaction time ~365 ms). Manipulandum position is monitored using a digitizing tablet sampled at 72 Hz.

3.1.2 Continuous tracking task: This task has been developed by our laboratory for a systems analysis approach to describe neural encoding in MI. It overcomes numerous shortcomings of step tracking tasks: correlation of kinematic variables and nonstationarities in behavioral and neural data. This makes it possible to treat each neural spike as an independent sample from a process with a known distribution, a requirement for many statistical tests and for information theoretic analysis. This task uses the same 2 dimensional device as the direction task except that the stimulus must be tracked in a continuous fashion. We generate a broad distribution of movement stimuli that monkeys must track. Data from this task are used to create the linear filters used to test our ability to reconstruct hand motion from neural data.

Our approach is to have the monkey move its hand (the end point effector) across a two dimensional workspace such that the probability distribution of each kinematic variable is as broad as possible (i.e. the monkey will make a series of motions that will, over time, include all possible velocities, positions, etc., within a plane of movement.) For this task monkeys are trained to track a visual target (2 degree white circle on black background) on a computer

screen. The target motion is computer controlled to move in a pseudorandom, experimenter determined fashion. The statistics of the motion of the target, and the resultant tracking motion of the monkey's hand, are chosen in such a way that the entropy (the accepted measure of "broadness") of the distribution of motion is maximized under the constraints imposed by reaction time and biomechanical properties of the arm. In other words, the monkey moves its hand so that we sample from the complete space of possible planar arm movements. We hypothesize that it will be possible to mimic the arm kinematics with a prosthetic device (robot arm) by building a series of decoding filters that defines the relationship between the set of kinematic variables and arm movement. Because we have simultaneously recorded neurons, we can use not only the firing rate of each cell, but also the joint or higher order distribution (e.g. covariance) of neuronal activity to extract information about natural, time-varying movement parameters

3.1.3. Button box task. The button task has been developed as a simple version of the radial task (3.1.1) task that can be learned quickly so that monkeys can be made available for testing arrays. Task training is the major rate limiting step to array implantation, since monkeys must be trained before this surgery occurs. This task simply requires the monkey to press one illuminated button arranged in a circle around a central button Buttons are illuminated with a red LED to indicate which button to press for a reward. During training monkeys are shaped to hold to the center button for a 1-4 second random delay, then one peripheral button is illuminated as the target and as a go signal. Successful pressing of the illuminated button is reinforced with liquid. The devices we have developed are introduced in the cage, then monkeys perform the same task in the primate chair, where recordings are performed. In Q7 three monkeys continued button box cage training. We also continued to make improvements on the button box training system, including plans to implement new hardware and software to maximize the effectiveness of the cage training. Two monkeys continued button box chair training, and one of these monkeys has successfully mastered the final button box task. One monkey continued training with the manipulandum, and learned a hold task and a tracking task. One new monkey also began chair training in preparation for button box chair training.

3.2 Array Implantation*:* Arrays are implanted in the MI arm representation, medial to the spur of the arcuate sulcus, abutting the central sulcus. The ability to locate arm related neurons using these sulcal landmarks has been 100% successful in our tests. The UEA microelectrode arrays consist of 100, 1.0mm long platinized tip, silicon probes arranged in a square grid on 400μm centers. Impedances between 50-500 kΩ (1 nA, 1kHz sine wave) (Nordhausen et al., 1996). Arrays are wired to connectors contained in a custom designed titanium percutaneous pedestal with using 1 mil gold, Teflon insulated wire (the assembly is custom fabricated for us by Bionics). Two extra wires (50.8 μm diameter, Pt-Ir 20%) with approximately 5.0 mm of the terminal insulation removed are inserted subdurally and used as reference and as backup. The bundle of gold wires is coated with silicone elastomer (MDX4-4210, Dow Corning, MI). The back of the array and percutaneous connectors are coated with silicone elastomer to mechanically protect the wires and maintain electrical insulation at the bond pad sites.

The array is inserted rapidly into the cortex using a calibrated, pneumatically propelled mass, and typically, the array is and cortical surface is covered by a Teflon sheet. The dura is then loosely closed and this area is covered by a sheet of Gortex followed by silicon elastomer.

Finally the entire region is covered with cranioplast cement which is anchored to the skull through a series of titanium bone screws. (see Figure 1.)

Array implantation procedures initially involved several foreign bodies, which are undesirable if arrays are to be implanted in humans, and have been the source of infection (between the acrylic and the bone) in cases, especially with long survival times of years. Foreign bodies in our earliest version of the implant procedure include placement of Teflon sheets above and below the dura, addition of silicone elastomere and most significantly the use of acrylic sealant. We have largely replaced the acrylic seal with a titanium mesh (Timesh) covering. Successful animal recovery has been achieved in every case and there is no evidence that this procedure affects recording quality or stability. We have continued to use Timesh and isolate the dura from the arachnoid membrane.

During the past quarter we implanted three arrays: two (bilaterally) in monkey 99-7 and one in monkey 99-3). Monkey 99-3 was used for a few recording but developed a subdural infection of unknown source. Antibiotic treatments were begun in response to signs of infection, but, upon the advice of the university veterinarian, it was decided to perfuse this monkey (tissue was saved for analysis of the type of infection). Monkey 99-7 has progressed without difficulty. One additional monkey (B001)with an implant more than a year in duration continues to be in excellent health and is used for array testing.

Implantation surgeries have proceeded with some challenges. Two difficulties encountered are (1) positioning of the array during surgery because the wire bundle is stiff and non compliant and (2) positioning of the reference wires, which are excessively springy. We have been discussing the need for a more flexible connect system with BTI, but it appears that this will require significant development time. For the reference wire, BTI will fabricate future arrays with larger diameter reference wires. During this quarter we delayed implantations in anticipation of the availability of new 100 channel compact connectors that are under development by BTI. Some delay was encountered in manufacture in testing by BTI, so one additional tulip style connector was implanted. (monkey 99-3).

3.3 Array development: Connector technology has severely limited the number of electrodes we able to use address for recording. The generally available connector from Bionics was a 12 pin Microtek, which allowed only connection to only 11 electrodes of the 100 available in the array. To increase recording to 22 we used two of these connectors. Subsequently we adopted a Winchester 50 pin connector. Five arrays with this connector type have been implanted in 4 monkeys (all before his contract commenced), but the connector is bulky and it is difficult to fabricate a pedestal that seats properly on the skull of different animals. BTI developed a new generation of 45 pin connectors, called the *tulip* connector, which is based upon an edge card connector. With two of these connectors we can achieve 74 connections (with two references). Three tulip-type arrays have been implanted this quarter (total to date of project = 8), This has been the only high density connector available in the project to date. These connectors have been problematic for several reasons. One is that the connector profile is high and the edge card is easily damaged. In addition the gold connections have a limited number of attachment, they are prone to wear. In this quarter two of the connectors failed. In one case we found that the connector had rotated in the pedestal, thereby shearing all of the wires. In the other case the gold contacts shorted to each other and recordings failed. New, low insertion force connectors have been devised by BTI and we are expecting delivery in Sept. 2001.

3.4 Array Testing *Impedance* High impedances have the advantage of providing high signal to noise ratio, but the tip must be close to a neuron to obtain recordings. On the other hand, a low impedance electrode detects many cells, making it difficult to isolate neurons from background 'hash'. The goal of this part of the project is to identify the optimal impedances for UE. We have systematically tested electrode impedances from 50 – 500 kΩ (~50, 100, 200, 500). Preliminary data indicate that impedance is not critical to obtain useful recordings, but they also show that the population of recorded neurons is unstable from day to day. These data will be correlated with impedance to identify the ideal impedance range. Impedance evaluation suggests that, for the BTI arrays, there is poor correlation between the ability to detect a single unit and electrode impedance over ranges between 100 and 800 kΩ.

Recording Stability: The ability to maintain the same cells each day of recording by the UA is not known and is important in the design of a prosthetic device. Decoding algorithms must be able to deal with instabilities. To measure stability similarity measures including the autocorrelation function (to determine firing pattern), movement related activity, directional tuning properties, and spike waveform. This data is being analyzed by Dr. Hatsopoulos and Dr. Kenji Nakata, a neurosurgical resident at Brown working in the lab during his research year. The data is being prepared for publication.

Our conclusion is that small numbers of electrodes have the same neurons each day, but that the majority of electrodes record new neurons in an unpredictable way over time. Over the course of one year, our data suggest that that the original population of neurons recorded is entirely replaced. The cause of this shift is unknown. In addition, Our analyses so far indicate that about 40% of the active electrodes are capable of recording useful neural activity.

Tethering Forces Original observations on the UEA suggested that the wire bundle from the array to the connector provided significant tethering forces, causing the electrode to move and, hence, damage the cortex. Our initial UEA versions were tested with only 11 of the 100 possible wires attached. We have now tested arrays with 11, 21, 47, or 74 wires have been attached to the 100 possible in the array. Across all of the experiments the yield of usable units has been ~30-40% of the active electrodes and this appears to be independent of the number of wires. Thus, we conclude that tethering forces are not a significant factor in determining electrode yield.

Head stabilization: Lack of head stabilization has created a number of difficulties in recording. Movement of some versions of the array connectors (notable the ribbon cable connectors to the preamplifiers) produce significant electrical artifact. Some monkeys rotate in the primate chair, which results in damage to the cabling. Consequently, we developed and implemented a new head restraint system. This has introduced some delays in implantation and testing because we needed to design and manufacture head posts and then implant each monkey. Head post surgery requires at least a six week period to allow integration of the posts into the skull. In addition, the initial version of the headposts had small bases that were not sufficiently stable. In this quarter we redesigned the head post base and fabricated them. Six monkeys have received headbolt implants prior to this period. During this quarter we implanted one additional monkey with head bolts for head stabilization during recording.

3.5 Histological analyses*:* The goal of histological analysis is to determine tissue reaction to the UIEA. We test for cell loss and reaction using both thionin cell stain and GFAP, to

test for glial reactivity. During this quarter we carried out qualitative examination of tissue from B164. This analysis indicates that there are minimal tissue effects of the array over time. Several months after implantation there is little glial reaction, as measured by GFAP reaction product. Long term biocompatibility is also demonstrated by the ability to record neurons for years on these arrays. By qualitative measures these neurons appear to be no different in their properties from those recorded in acute preparations. Current arrays do however, sink 100 or more μm into the cortex, compressing the upper cortical layers; the functional effect of this is not detectable in our neural recordings. Two monkeys with arrays were perfused the quarter (99-8 and 99-7). Tissue blocks were sent for histological processing by an outside vendor**.**

3.6 Recoding Technology Development. We are working with Dr. Richard Normann's group at the University of Utah to modify one of the Bionics 100 channel recording/acquisition systems so that it can classify spikes in real time and provide output to a second computer. A second computer is used to decode the spike patterns, both to build movement classification models and for online classification. Working with Richard Normann and BTI we modified the current BTI spike acquisition device so that it is capable of providing 'spike times' in real time to the decoding computer. We have now adapted a Plexon data acquisition system for tests of real time spike control because it already has real time , sorted spike capability and it overcomes certain limitations of the BTI. Plexon is able to set up more rapidly for online classification, and most importantly only the Plexon can provide discriminated spike events to another computer in real time. Further advantages of the Plexon is that is has a higher sampling rate for more accurate spike discrimination and that it can output single, discriminated spike times.

4. NEURAL DECODING

The goals of this aspect of the project are to determine: whether we can recover the hand trajectory using the activity of multiple MI neurons; how reliable this reconstruction will be; how many simultaneously recorded neurons are required; can the computation be performed fast enough to be used in a prosthetic device; and finally can the reconstruction algorithm be made adaptive enough that it will withstand changes in the functional properties of recorded neurons as may result for instance from motion of the implant between successive days or weeks (see above). In a first step, we have demonstrated that linear regression methods based upon small numbers of neurons provide a moderately accurate estimate of any new hand trajectory. This work is brine submitted for publication. In a second step we developed non-parametric Bayesian methods with the goal of achieving better trajectory reconstructions. The provisional conclusions of our study at the present time, based on partly simulated data, suggest that simultaneous from several hundred cells, when they are available, will provide very accurate reconstructions of hand trajectory.

Previous work has shown that neural discharge in motor cortex is related to a number of kinematic variables, including direction, position, acceleration and velocity (Georgopoulos and Ashe, 1994; Fu et al., 1993). However, these analyses have been restricted to simple evaluations of discrete, usually scalar, variables studied in tasks in which monkeys must only move from a single point to one of a few static targets; We term this a discrete (as opposed to a continuous tracking task). Because of technical limitations, cells in these earlier studies were recorded one at a time. Information underlying cortical movement control contained in the mutual activity of populations of neurons is not available from the available single electrode data; extraction of this information requires observation of not one, but many

simultaneously recorded neurons. Further, just as the visual or auditory processing can not be described by single discrete parameters, the rich structure and fluidity of natural movements can not be captured by specifying, for example, average direction of hand motion over hundreds of milliseconds. Neural control of movement proceeds continuously, and satisfactory description of natural movements requires simultaneous knowledge of multiple time-varying parameters; we term tasks that require continuous movement under visually guided or internal control *continuous tasks*.

4.1` Linear Decoding: This approach consists in regressing separately the *x* and *y* coordinates of hand position (or velocity) at time *t* on the observed spike counts of the simultaneously recorded neurons in a window of variable length around time *t*, suitably discretized. For instance, by discretizing a window of length 1sec into bins of length 50ms each, we get 20*N* explanatory variables, where N is the number of neurons. Mathematically and computationally, this regression is straightforward: it simply solves for the least-squared-error linear solution. This allowed us to explore systematically the quality of the reconstruction that this method provides for a wide spectrum of discretization schemes, ranging from 1 to 30 bins around time *t*, with either identical or different widths (allowing, in particular, a finer resolution near time *t*). We used both causal and non-causal schemes (in the former, observations are allowed only before time t).

The performance of this linear filtering method has been assessed by cross-validation, using three different criteria: the L2 distance between the observed and the reconstructed positions; the fraction of the variance of the observed position accounted for by the reconstruction; the correlation coefficient between the observed and reconstructed positions. It is not clear which of these is optimal and methods of error evaluation are being investigated.

4.2 Non-Parametric Decoding Algorithms The simple linear-filtering approach mentioned above does not provide a probabilistic interpretation of the data that can facilitate analysis and support the principled combination of multiple sources of information. Previously used probabilistic approaches such as Kalman filtering do not suffer from this drawback, yet it should be noted that with a small number of cells our interpretation of the neural data may be ambiguous and the posterior probability of the kinematic variables, given the neural activity, may be best modeled by a non-Gaussian, possibly multi-modal, distribution. Clearly, Kalman filtering is inadequate under these conditions, and a non-parametric approach is called for. Thus, to cope with these issues in a sound probabilistic framework, we started to investigate a non-parametric approach that uses factored sampling to discretely approximate the posterior distribution, and particle filtering to propagate and update this distribution over time (Isard and Blake 1998).

Estimating the Conditional Firing Maps We view the neural firing activity recorded during training as a stochastic and sparse realization of some underlying model that relates neural firing to hand motion or hand position. Each plot (for a given cortical cell) can be thought of as a type of "tuning function," or "receptive field," which characterizes the "response" of the cell given hand velocity or position. However, since the data is very noisy and sparse, we need to compute an optimal estimate of these receptive fields by an appropriate smoothing of the "training" data.

In previous work, investigators have considered a variety of strict models of the tuning function of neurons, including a cosine tuning function (Georgopoulos et al. 1986)

and a modified cosine function (Moran and Schwartz 1999). We have explored various non-parametric approaches to model a neurons properties and, adopting a Bayesian formulation, constructed a Maximum *A Posteriori* (MAP) estimate of a cell's conditional firing. In this case we use data from the cell's firing itself to determine a probabilistic model of the cell's tuning function, rather than assume some strict model. The data for this approach requires the broad sampling produced by the continuous task; the non-stationarities and irregular sampling of discrete tasks are not sufficient or appropriate to generate statistical representations of the tuning functions. We compare the various models using cross-validation to test against the ability of the decoding schema to deal with any set of new data. . It is expected that this approach will provide a richer movement signal than can obtained in parametric models and will allow the use of statistical methods to evaluate how well the decoding performs.

Our non-parametric models are related to Markov Random Fields (MRF) (Geman and Geman 1984), and include a spatial *prior* probability, which encodes our expectations about the variation of neural activity in velocity or position space. The MRF prior states that the expected firing at a given velocity depends only on the firing at neighboring velocities. We consider two possible prior models: Gaussian and "robust." A Gaussian prior corresponds to an assumption that the firing rate varies smoothly. A robust prior assumes a heavy-tailed distribution of the spatial variation, and implies piecewise smooth data. Our models also include a term that represents the *likelihood* of observing a particular firing rate given the true (i.e., to-be-estimated) rate. We compared two such "generative" models of the spike count within 50 ms: a Poisson model and a Gaussian model.

We fit these various models—cosine, modified cosine (Moran and Schwartz 1999), Gaussian+Gaussian, and Poisson+Robust)—to the training data. In the case of the Gaussian+Gaussian and Poisson+Robust models, the optimal value of the parameters is computed for each cell using cross validation. The solution to the Gaussian+Gaussian model can be computed in closed form but for the Poisson+Robust model no closed form solution exists and we derived an approximate solution using an iterative procedure.

We are currently performing extensive comparisons of these different models using cross-validated log-likelihood and other criteria.

Temporal Inference In this step, we infer a posterior probability distribution over arm motion conditioned on a sequence of neural test data using Bayesian inference. The learned firing models of multiple cells are used to define a non-Gaussian likelihood term which is combined with a prior probability for the kinematics. A particle filtering method is used to represent and propagate the posterior distribution over time. We assume that the temporal dynamics of the states form a Markov chain for which the state at a given time depends only on the state at the previous time instant. We then use Bayes rule and a Poisson likelihood, whose mean is the one estimated as described above. We model the dynamics of the hand velocity as a diffusion process, and represent the posterior distribution with a discrete, weighted set, of 3000 random samples which are propagated in time using a standard "particle filter" (Isard and Blake 1998).

It is important to note that, unlike in previous applications of particle filtering, the likelihood of firing for an individual cell in 50 ms provides very little information. For the posterior to be meaningful we must combine evidence from multiple cells. Our experiments indicate that

the responses from our 24 cells are insufficient for this task. To demonstrate the feasibility of the particle filtering method, we synthesized up to 1000 cells by taking the learned models of the 24 cells and translating them along the movement-direction axis to generate a more complete covering of the velocity space. Note that the assumption of the existence of such a set of cells in MI is quite reasonable give the sampling of cells we have observed in multiple monkeys. (However, the firings of these cells need not be independent, which may affect the validity of our conclusions.) From the set of synthetic cells we then generate a synthetic spike train by taking a known sequence of hand velocities and stochastically generating spikes using the learned conditional firing models with a Poisson generative model. Particle filtering is used to estimate the posterior distribution over hand velocities given the synthetic neural data. This Bayesian approach, when compared with traditional linear filtering methods, appears to provide probabilistically sound, causal, estimates in short time windows of 50ms, whereas linear filter approaches use long time windows. These results suggest that probabalistic methods will be useful for rapid, accurate generation of control signals that can be statistically evaluated during neural prosthetic applications. This work was submitted as a paper to the Neural Information Processing Meeting for 2001.

4.3 Further issues We expect that after the model(s) is (are) suitably trained we will be able to control the movement of the robot arm in real time, using the decoding provided by the model, i.e., the most likely sequence of states that is computed and continuously updated given the observed simultaneous spiking processes. One problem may be occur if the set of neurons changes during the course of day-to day testing. Using probabilistic decoding we can establish real time checks of the decoding reliability. If error bounds are exceeded, we can initiate a recalibration sequence. This will be part of future efforts.

5. Interface development

The goals of this aspect of the project are (5.1) to develop interfaces with peripheral devices (i.e., robot arm, computer), (5.2) demonstrate that decoded neural signals can be used to control such peripheral devices, and (5.3) demonstrate that monkeys can bring this signal under near real time control. In this quarter we continued to develop software that will transform hand trajectory coordinates into signals that move position cursors on a computer monitor and our CRS robot arm. We have shown that a robot arm or computer cursor can be used to mimic actual hand motion using data processed offline. The quarter we also tested the ability for a monkey to control a device using neural signals to substitute for hand motion. Lastly began experiments to begin to test the ability for a monkey to bring a device under control when the arm is paralyzed. The purpose of this last step is to demonstrate that neural control can be obtained in the absence of any sensory input form the arm or motor output to the arm

5.1 Interface with peripheral devices. We have designed interfaces that allow decoded neural signals to be used as a control input to other devices. An interface that couples the signal to a PC is complete and work is ongoing to complete an interface with a CRS robot. During this period the output of Labview programs was successfully coupled to the CRS robot arm to provide a command signal to the controller box.

5.2 Offline control of prosthetic devices*:* During this period Ammar Shakouni, an engineering MS student, wrote software in Labview to transform the neurally decoded trajectory signals into commands for the CRS robot arm with data streamed from another computer. We have encountered difficulties in trying to update the robot

position at appropriate time intervals using this system The CRS robot position control hardware is designed with a speed control that must processed at each position update. This is time consuming and generally useless since the properties of the arm and the rapid updating (~100 ms) make it reasonable to simply move the arm at each step at its maximum speed. The robot's hardware interface appears to create delays and variability in executing instructions. We are investigating methods to overcome these problems.

5.3 Real time Control of prosthetic devices: During this period we trained a monkey to use the two-dimensional linear filter reconstruction signal to acquire targets displayed on the video monitor. Filters were built rapidly using neurons recorded in real time and the monkey was able to use the signal immediately to control cursor motion. The monkey did not receive any visual feedback about his actual hand position: only the predicted hand position from neural activity was displayed. Whereas Euclidean distance and correlation coefficients are suitable for measuring how well linear filters reconstruct actual trajectories in offline analysis, measuring neuroprosthetic use in a closed-loop system calls for measures that pertain directly to functional utility. We chose a task in which stationary targets would appear at a random position on the screen and the animal had to move the cursor to the target to receive a reward and be presented with the next target. We found that the time-to-target (time from appearance of target to acquisition of target) was a helpful functional measure: the time-to-target using neural control was not statistically significantly different from time-to-target with manual control by a one sided Kologorof-Smirnof one-sided test (alpha = 0.05). In addition to controlling the cursor, the prediction signal was also used to control a remotely located F5F3 robotic arm (CRS Robotics) using two LabView programs coupled by the ethernet. We successfully implemented ~real-time control of the robotic arm from a neuroprosthetic algorithm signal.

5.4 Arm paralysis/Control without feedback. The goal is to demonstrate that monkeys are able to control the robot arm using neural activity when arm actions are impossible and sensory feedback is missing, a condition that mimics human paralysis. This will be achieved by blocking the brachial plexus with injection of sodium channel blockers (lidocaine, Klein et al., 1998). This procedure can be used reversibly to eliminate all movement and sensation from the arm for a period of hours. The method is used safely and repeatedly in humans for surgical procedures as well as chronically (Lierz et al., 1998), so it represents minimal risk to the health or well being of the monkey. It is a reasonable substitute for arm amputation which is a more invasive way to demonstrate that motor cortical neural activity can be used for control when the effector member is missing. For testing, a monkey trained to position a computer cursor in our tracking tasks will receive a brachial plexus blockade. Then the monkey will be presented with the visual display and feedback. Cursor position will be controlled using the neural output, based upon a set of linear filters built from task performance immediately before arm paralysis. During the past quarter, in consultation with the University ACF veterinarian, James Harper, we decided to implant an injection port in the back with a cannula leading to the axilla to achieve a means to deliver injections repeatedly with minimally invasive methods used routinely in humans. We implanted one animal with a reservoir(sutured to subcutaneous tissue and muscles on caudal scapula) attached to a catheter anchored in the middle of the brachial plexus ipsilateral to the reservoir. This enables us to acutely inject lidocaine that will reach the desired target. This surgery was performed without significant difficulty and the animal recovered well. The first

attempted injection through the port produced no effect. Radio opaque dye was injected into the reservoir and an X-ray taken, but the films were inconclusive. The cannula placement was examined in a second surgical procedure and found to be dislocated from its original position and encased in a fibrotic tunnel. It was cleaned, repositioned and sutured into place. The second injection produced marked paralysis of the arm, without significant reaction from the monkey. However, within days the cannula again become blocked. We are now planning in the next quarter to attempt a direct injection approach to achieve anesthesia successfully, since the cannula seems to become blocked by tissue ingrowth.

6.0 Plans For Next Quarter

1. Array Development

- **Behavioral Training:** There are currently 7 contract monkeys being trained for implantation and array testing.
- **Button box task** Button boxes software will be completed and a new computer interface will be completed that will allow control of cage trainers by one computer. Three monkeys will be trained to perform the radial task using this apparatus. We will make improvements in the button box software and make alterations in the hardware to increase the number of button boxes running at the same. Three monkeys will continue being trained to perform the radial task using this apparatus, and two more monkeys will begin training for the first time. Two monkeys will continue chair training with the button box for recording purposes.
- **Radial task & Continuous tracking.** Two monkeys are continuing to train in these tasks for recording purposes, 5 additional monkeys are being trained in these tasks for future implantations.
- **Arrays/implantation & Surgical Procedures** We are scheduling several array implantation surgeries in anticipation of delivery of a new 100 pin connector (expected 9/21/01) from Bionics which will allow us to record from all 100 electrodes; in addition this connector appears to have a number of other features (such as a low profile and durability) which will make it much more suitable as a long term implant. The first array of this type is expected at the end of September 2001 and additional arrays will be delivered in October.
- **Array development.** The major advance in array development in the next quarter will be the testing of the new connector. If surgical procedures can be performed during the next quarter, we expect testing of these arrays to begin by in the late part of the next quarter.
- **Array testing** We will continue to recording s from the one monkey that has high quality recordings and continue recordings from the monkey implanted in Q7. In addition we will begin testing the quality of recordings in monkey 99-3.

Perfusion histology We will examine processed tissue from two monkeys that were perfused in Q7. Processed tissue is expected to be available during this quarter.

2. Neural Decoding

a. **Linear Reconstruction;** We will test the day to day stability of linear decoders by using filters established on one day for the next days data set. We will complete and submit a manuscript on this work.

b. **Other methods;** Drs. Bienenstock and Black will continue to evaluate methods that use probabilistic inference to decode neural activity, as described in our NIPS manuscript

3. Interface Development

a. **Peripheral devices interfaces.** Mr. Shakouni will complete and improve software to drive the robot arm ;and will determine the sources of time delay and variability.

b. **Offline control Completed.**

c. **Real Time control.** Mr. Serruya will continue to evaluate the ability for monkeys to control a position feedback cursor for a behavioral task. We will continue with monkey B001 and begin testing of monkey 99-3 who received an array during q7.

d. Arm paralysis/control without feedback. We will test direct injection methods to achieve arm paralysis. This will replace the indwelling catheter method that appears to block with fibrous tissue so rapidly as to be impractical to use. Dr. Emery Brown of Harvard Medical School, will provide assistance us in implementing methods that allow us to safely inject local anesthetic into the brachial plexus. We hope to adapt the anterior approach to reversible brachial plexus block used in pediatric emergency care.

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